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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/980,727
Filing Date: July 08, 2002
Appellant(s): REIN ET AL.

William J. Thomann
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/29/2010 appealing from the Office action mailed 10/19/2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

1, 5-6, 10, 16-18, and 20-32.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has a comment on the copy of the appealed claims contained in the Appendix to the appellant's brief. The claims appendix is not accurate with the current claims. The changes are as follows:

Claim 4 was cancelled in the amendment to the claims filed 10/22/2008. Furthermore in the amendments to the claims filed 10/22/2008 claim 1 was amended to include the limitation "and wherein up to 15% by weight water is added to the composition prior to co-extruding".

(**8) Evidence Relied Upon**

EP 0,580,860 A1	**Nakamichi et al.**	**5-1994**
WO 92/15285	**Lentz**	**9-1992**

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 10,16-18,23-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamichi *et al.* (EP 0,580,860 A1).

Nakamichi teaches a method of manufacturing a pharmaceutical solid dispersion by the use of a twin screw type extruder. See abstract. The solid dispersion was produced without heating chemicals and polymeric carriers above their respective

melting points. The polymeric carriers included virtually any natural or synthetic polymers including starch and processed starch. See page 3 lin 8-19. The drugs which could be incorporated into the dispersion were not particularly limited and the specification listed numerous examples. See page 4 lin 1-page 6 line 48.

Claims 10,16-17,23-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Lentz *et al.* (WO 92/15285).

The Lentz *et al.* document discloses controlled-release starch compositions (See Abstract). The compositions comprise a melt made from a starch/water mixture and an active ingredient. The starch is processed in such a way as to eliminate a granular starch structure, rendering it "destructured", which can include heating the starch melt above the glass transition temperature (See Page 11, Line 8 to Page 12, Line 30; and Page 17, Line 34 to Page 18, Line 15). This composition is processed under shear at temperatures ranging from about 80°C to about 240°C (See Abstract). This allows for greater compressibility in the formation of tablets (See Page 15, Lines 8-14). Various types of drugs, either water-soluble or -insoluble, may be incorporated into the disclosed controlled-release starch matrices (See Page 15, Line 25 to Page 16, Line 39). Various types of dosage forms, including tablets, capsules, beads, granules, powders, and solids may be formulated from the compositions. Processing techniques that may be used to produce such dosage forms include wet and dry granulation, injection molding, thermoforming, extrusion, co-extrusion, and cast molding (See Page 26, Line 29 to Page 27, Line 21). Release profiles are given which show the release of an active

ingredient over a period of 24 hours. The release profile of the active ingredient appears to follow a lapidus function (See Figures 2 & 3).

Although the disclosed release profiles only show drug release up to a period of 24 hours, the amount of drug released in some figures remain under 100%. It is the position of the examiner that the drug release can be extrapolated beyond 24 hours due to the insolubility of the amorphous starch matrix. The instant claims are thus anticipated.

Claims 1, 5-6, 10, 16-18, and 20-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakamichi *et al.* (EP 0,580,860 A1).

Nakamichi is disclosed above. Namamichi is silent on the specific temperatures of the extruder during the extruding process and the amount of water added to the mixture during processing. Nakamichi does disclose however that processing parameters such as pressure, temperature, feed rate of material, amounts of water, plasticizer and other additives are dependent on the type of drug and polymer, the twin screw extruder model used and other conditions. See page 3 lin 24-29. Nakamichi further discloses that it is important to select a combination of parameters such that the drug, polymer ect. will be maintained at temperatures below their decomposition points and vary the operating parameters according to the desired characteristics of the product. Thus the temperature of the extruder and amount of water added to the mixture to be extruded is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would

be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal temperature of the extruder and amount of water added to the mixture to be extruded in order to best achieve the desired characteristics of the product. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of temperature and amounts would have been obvious at the time of Applicant's invention. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969).

Claims 1, 5-6, 10, 16-18, and 20-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lentz *et al.* (WO 92/15285)

The Lentz *et al.* document discloses controlled-release starch compositions (See Abstract). The compositions comprise a melt made from a starch/water mixture and an active ingredient. The starch is processed in such a way as to eliminate a granular starch structure, rendering it "destructured", which can include heating the starch melt

above the glass transition temperature (See Page 11, Line 8 to Page 12, Line 30; and Page 17, Line 34 to Page 18, Line 15). This composition is processed under shear at temperatures ranging from about 80°C to about 240°C (See Abstract). This allows for greater compressibility in the formation of tablets (See Page 15, Lines 8-14). Various types of drugs, either water-soluble or -insoluble, may be incorporated into the disclosed controlled-release starch matrices (See Page 15, Line 25 to Page 16, Line 39). Various types of dosage forms, including tablets, capsules, beads, granules, powders, and solids may be formulated from the compositions. Processing techniques that may be used to produce such dosage forms include wet and dry granulation, injection molding, thermoforming, extrusion, co-extrusion, and cast molding (See Page 26, Line 29 to Page 27, Line 21). Release profiles are given which show the release of an active ingredient over a period of 24 hours. The release profile of the active ingredient appears to follow a lapidus function (See Figures 2 & 3).

Although the prior art does not explicitly disclose the limitations related to feed, screw, and die temperatures, it is the position of the examiner that the manipulation of such parameters would be well within the skill of one of ordinary skill in the art. One of ordinary skill in the art would be motivated to tailor such parameters, since such parameters have a direct impact on the release characteristics of the dosage forms created by the disclosed process. With this knowledge in mind, such processing temperatures may be adjusted as needed to create dosage forms with particular release profiles to suit a particularly desired application (See Example 11 in Lentz *et al.*). Therefore, the instantly claimed invention as a whole is *prima facie* obvious

(10) Response to Argument

The examiner notes that claims 1,3,5,6,8,10 and 12 are drawn to a co-extruded controlled release matrix comprising starch and a pharmaceutically active agent. The claims depend upon claims 1,4,5,20,21 or 22, which are method claims drawn to a process of producing the co-extruded controlled release matrix. The processing steps recited are that during the extrusion process the temperature of the extruder's orifice is below 100°C, under normal pressure, under sheer force and up to 15 wt% water is added. In order to overcome the prior art rejections appellants must show that their processing technique is different than the prior art and if the processing technique is different than a patentable distinction from the compositions of the prior art must result from the processing technique. Claims 1,3,5,6,8,10 and 12 are product by process claims. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

The examiner does not believe appellants have overcome the prior art rejection over Nakamichi because the reference discloses co-extruding starch and pharmaceutical together and exemplified temperatures at the orifice of the extruder below appellants claimed upper limit of 100°C. The processing technique of Nakamichi is the same, thus a product containing the same materials processed from such method

would make the same processed starch. The Lentz reference for similar reasons also anticipates claims1,3,5,6,8,10 and 12 because the processing technique is the same or obvious and the product made is within appellants claimed scope.

Appellant's first argument against the 35 U.S.C. 102(b) rejection over Nakamichi is that the solid dispersions of that reference are not controlled release as shown by the figures 1,3,5,6,8,10 and 12.

The figures described by appellants are only reprehensive of a few of the examples within Nakamichi, which were given solely for the purpose of illustration and were not to be construed as being limiting to their invention since many variations are possible without departing from the spirit and scope of the invention. Test example 7 has a nearly linear release profile over time, therefore it is not an immediate or delayed release formulation. Lastly since Nakamichi encompasses the same types of compositions as presently claimed it is inherent that the same composition will have the same properties including its release profile.

Appellants assert that test example 7 of Nakamichi uses a plasticizer which is not required in their present claim set.

The transitional term "comprising" used in claim 1, from which claim 10 is dependent upon does not exclude additional elements from being present in the formulation, thus the use of a plasticizer is not precluded from the claims. The transitional term "comprising", which is synonymous with "including", "containing", or "characterized by", is inclusive or open ended and does not exclude additional elements

or method steps recited in the prior art. Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003).

Appellants assert that Nakamichi does not describe a vitrified product.

It is noted by the examiner that vitrified is not formally defined within appellant's specification. In their arguments appellants state that vitrified mean glassy (see page 15, second paragraph lines 8-9) and the specification only states that "corresponding dosage forms with controlled release may be produced by partial to complete vitrification, i.e. by transition into the amorphous state of the polysaccharide-containing mixture under suitable extrusion conditions". See specification page 6, 2nd paragraph lines 9-13. Thus from the disclosure of the specification vitrified used in this manner seems to describe a polysaccharide (starch) which is amorphous after extrusion and from appellants comments they intend vitrified to mean glassy. Appellants have not described how the extruded product of Nakamichi would not be vitrified, i.e. transition into an amorphous state under the extrusion conditions described or glassy. It is noted by the examiner that several examples describe extrusion temperatures below or just at appellants claimed upper limit of 100 °C in claim 1. Based upon the extrusion temperatures described by Nakamichi which are either below or at the claimed orifice temperature upper limit it is not unreasonable to presume that the extrusion process of Nakamichi would necessarily result in a so called vitrified product, i.e. glassy or transition into the amorphous state of the polysaccharide-containing mixture. **The examiner notes that test example 7 was obtained from example 5 in which an**

extruder barrel temperature of 80°C was used, lower than appellants claimed upper temperature limit.

Appellants argue that the active ingredient within Lentz is not processed with the starch but is merely combined with the starch after processing.

The examiner disagrees with the above assertion; Lentz clearly teaches that the active ingredient may be added to the starch prior to destructurization process (the processing step of the starch). See page 13 lines 5-22 of Lentz.

Appellants assert Lentz product is soft and rubbery and is thus above the glass transition temperature. Appellants further assert that Lentz prefers to process the composition above the glass transition temperature of the starch, which is said to be in contrast to their own claimed invention were the temperature never exceeds the glass transition temperature.

In regards to appellants assertion that the product within the examples is soft and rubbery, this argument is not found persuasive since the examples within Lentz were given solely for the purpose of illustration and were not to be construed as being limiting to their invention since many variations are possible without departing from the spirit and scope of the invention. Clearly Lentz describes that the starch could be in several physical forms depending on the processing temperature including melts and/or thermoplastic materials which would not be physically rubbery or soft, rather upon cooling they would be glass-like. As evidence the examiner relies upon the definition provided on Wikipedia, a definition that is supported by references, which states a

thermoplastic is a polymer that turns to a liquid when heated and freezes to a very **glassy state** when cooled sufficiently. http://en.wikipedia.org/wiki/Thermoplastic. Secondly Lentz teaches a range of temperatures to process the starch and specific examples within the experimental section describe processes that are within appellants claimed temperature range, see example 11 page 34-35. It is also noted by the examiner that claim 6 states the shear force, temperature and pressure are modified to achieve glass transition of the starch, thus it would appear that appellant's matrix should be processed at the glass transition temperature.

Appellants further argue that the declaration filed 2/12/2007 shows that processing the starch over 100°C leads to a formed product.

Lentz exemplifies and describes a range of temperatures below 100°C, appellants must consider the entire teaching of Lentz not just the portion that describes processing techniques that are not within their claimed scope.

Appellants argue that figure 6 of Lentz shows that tablets with a water content less than 15.8 wt% are not controlled release which is said to be in contrast to their claimed invention which requires a water content less than 15 wt%.

The examiner notes that appellant's limitation of adding less than 15 wt% water in claim 1 during processing is not limiting the amount of water in the final product formed by extrusion process. The amount of water present after mixing and extruding will be different than the amount of water added since some of the water added will be lost during the extrusion process and water is naturally present in the starting materials. As described in example 1 of Lentz water is naturally present in the starch used (potato

starch having a water content of about 15-20 wt%). Furthermore figure 6 is taken from just one example and the examples of Lentz were given solely for the purpose of illustration and were not to be construed as being limiting to their invention since many variations are possible without departing from the spirit and scope of the invention. Lastly the examiner notes in fig 6 that the formulations with less than 15.8 wt% water were still controlled release in that they delivered the active over a time period of up to 6 hours, releasing an active ingredient up to 6 hours is not considered an immediate release dosage form.

With regard to the 35 U.S.C. 103(a) over Nakamichi appellants assert the reference does not provide the skilled artisan a teaching or suggestion of the product obtained or which extrusion parameters to adjust such as temperature, pressure and water and how to adjust such parameters. Appellants assert it would be undue experimentation to achieve the claimed invention based upon the teachings of Nakamichi.

The examiner respectfully disagrees. Nakamichi discloses that the temperature used during processing should be below the decomposition points of the ingredients within the composition such as the drug, polymer, etc. Thus there is clear disclosure within the reference on the importance of optimizing temperature during processing to avoid decomposition. Furthermore as noted above the temperatures exemplified are either at or below appellants claimed upper limit of 100 ^{o}C. Nakamichi also describes how aqueous solution lowers the transition temperatures of polymer, allowing the

molding temperatures to be set lower in order to prevent thermal degradation of the polymer and drug. Thus there is also a disclosure within the reference and a reason to adjust the amounts of aqueous solution during the processing of the composition. As clearly described within Nakamichi the parameters of temperature and water added are adjusted in order to prevent thermal decomposition and adjusting these parameters would not be undue experimentation since the methods of adjusting them would be routine and ordinary to one of ordinary skill in the art. The processing of Nakamichi is presumed to be done at standard or normal pressure (room pressure, 1 ATM), since the reference is silent with respect to adjusting the pressure during processing.

With regard to the 35 U.S.C. 103(a) over Lentz appellants reiterate their arguments from the 35 U.S.C.102 rejection over the reference; that is the active is combined with the active after processing and the product is soft and rubbery and therefore Lentz heats the starch above the glass transition temperature. The examiner incorporates his response from above, as noted above these arguments are not found to be persuasive.

Appellants reiterate their argument above in regards to the declaration filed 2/12/2007 which shows that processing starch over 100°C leads to a formed product. Appellants further argue that the declaration by Dr. Rein details how the temperature range of 80-240°C for processing described in Lentz does not take place at any temperature between 80-240°C, rather the entire process occurs at temperatures encompassing 80-240°C never just 80 °C. Appellants further argue that since the

processing temperatures of Lentz are above the glass transition temperature the product cannot be vitrified, i.e. glassy.

Lentz exemplifies and describes a range of temperatures below 100°C, appellants must consider the entire teaching of Lentz not just the portion that describes processing techniques that are not within their claimed scope. Clearly Lentz does teach an overlapping temperature range for the temperature of the orifice and there are specific examples in figure 10 in which the processing temperature for the controlled release formulation was 100 °C and 70°C, this example shows that contrary to appellants declaration the processing was carried out at either a constant temperature or at least a final temperature that is at or below appellants claimed upper limit of 100 °C. With regards to the product being vitrified since the processing technique of Lentz is obviously within or overlapping appellants claimed extrusion parameters the product made will be the same, i.e. it will be glassy. Furthermore Lentz describes that the starch could be in several physical forms depending on the processing temperature including melts and/or thermoplastic materials which would not be physically rubbery or soft, rather upon cooling they would be glass-like, see evidence provided by Wikipedia.org.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/James W Rogers/

Examiner, Art Unit 1618

Conferees:

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612